EDITORIAL (SEE CHENG ET AL., P. 2027)

Can We Become Victims of Our Own Success?

The last 5 years seem to have marked a transition in the history of diabetes care. Whereas for two decades we have preached the importance of good glycemic control to manage the risk of diabetes-associated complications, the truth of the matter is that rarely did patients with diabetes achieve target A1C levels <7%. As reported in *Diabetes Care* in 20008 in an analysis of the National Health and Nutrition Examination Survey (NHANES) dataset, the odds ratio (OR) of people with diagnosed diabetes achieving an A1C <7% had increased 2.5-fold between 1999–2000 and 2003–2004. Most impressively, the average A1C among those treated with diet alone over the same interval had decreased from 7.04 to 6.07%, with 89.7% having an A1C <7% (1). Undoubtedly, this improvement is due in part to improved comprehensive management of diabetes as a result of better access to diabetes education and nutrition services, the rapid advances in the pharmacotherapy for diabetes, and better screening and diagnosis of diabetes. As reported in *Diabetes Care* in 2009 using the NHANES dataset, though the prevalence of diabetes continues to rise, it is clearly being recognized more frequently (2).

In this issue, Cheng et al. (3) present another masterful analysis of the NHANES dataset. The study examines the relationship between two measures of glycemia (A1C and fasting plasma glucose [FPG]) and the prevalence of retinopathy in 1,066 individuals 40 years of age or older in the 2005–2006 NHANES dataset. After excluding those individuals who were using hypoglycemic medications, the glycemic levels above which the prevalence of retinopathy "took off" were A1C 5.5% and FPG 7.0 mmol/l (126 mg/dl). Furthermore, A1C was a better predictor of retinopathy risk than FPG, determined by receiver operator curve analysis. The authors suggest that this analysis has implications for diagnostic thresholds for diabetes. This is a critical issue because there has been an increasing call over many years for a diagnostic strategy using A1C, and a recent recommendation suggests that an A1C of 6.5% is an appropriate diagnostic threshold based in large part on a similar analysis of 28,000 subjects from nine countries in the Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance study (DETECT-2) pooling project (4).

The authors point out that other datasets have suggested other diagnostic thresholds of A1C for diabetes. The discussion is excellent, and a variety of potentially confounding factors are explored, primarily differences in A1C assay used and differences in techniques for assessing and defining retinopathy. Fortunately, at least in future studies, A1C assays have been standardized internationally to a much greater extent than glucose assays. The ideal study design to examine how best to make the diagnosis of diabetes would be a prospective cohort study in which the rates of incident retinopathy could be examined over time in a large population of nondiabetic individuals.

The current report is relatively small, increasing the potential for a spurious result. The population does reflect the population of the U.S. and therefore is arguably most appropriate for determining diagnostic strategies for our uniquely multiethnic and overweight population. The current study uses a very sensitive definition of retinopathy that would tend to be less specific and therefore perhaps suggests a lower threshold than a less sensitive, more specific definition.

However, I wonder if the fundamental reason that the current report suggests such a low threshold for the development of retinopathy is that the data are exclusively collected in 2005–2006 and include data from people with known abnormalities of glucose metabolism—people with both diabetes and other related abnormalities such as impaired fasting glucose, impaired glucose tolerance, and metabolic syndrome who have been counseled to make lifestyle changes to reduce glycemia.

Thus, the A1C data for 2005–2006 in the NHANES study may reflect not the peak A1C of a lifetime of gradually increasing insulin resistance and declining insulin secretion but a new lower level attained as a result of our success in managing risk in the overweight with abnormalities in glucose, lipids, or blood pressure. This is suggested by the remarkably low level of A1C among people with diagnosed diabetes treated with lifestyle management in 2003–2004 presented above. If the average A1C among lifestyle-treated people with diabetes was ~6%, almost certainly they had a higher A1C at some point in their life. Great analytical caution is necessary to avoid the nearly inevitable pitfalls of examining a population with diagnosed diabetes to decide what the appropriate cut point for the diagnosis should be based on the presence of a complication that clearly developed at some time prior to enrollment in the study. With improving screening and control, we may otherwise fall victims to our own success in an endless spiral of more intensive medicalization.

Whether abnormalities of glycemia are diagnosed with A1C in the future at an A1C of 5.5%, as implied in the current report, 6.0% (5) or 6.5% (4) will directly affect the lives of many tens of millions of people in the U.S. alone and perhaps hundreds of millions of people worldwide. Those at lower risk because of more normal baseline glycemia theoretically are at lower risk of complications, and thus the potential benefit from their identification will come at a higher price both personally and societally. These decisions will have an enormous and foreseeable impact on health care systems and costs.

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